Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Ambrisentan

Evidence Summary

Though ambrisentan has never been studied in an Alzheimer's model, evidence for contribution of the endothelin system in cerebral hypoperfusion is intriguing and worthy of future study.

Neuroprotective Benefit: No evidence suggests that ambrisentan is beneficial in Alzheimer's disease; however, evidence suggests that ET1 is increased in Alzheimer's or before disease onset suggesting a hypothetical benefit.

Aging and related health concerns: In general, it is unclear whether ambrisentan will be beneficial in most age-related disease. However, it might be beneficial in certain age-related conditions where serum pro-ET1 or ET1 levels are increased.

Safety: Peripheral edema is a common side effect with ambrisentan. Other potential side effects include nasal congestion and anemia.

What is it?

Ambrisentan is an endothelin A (ETA) receptor antagonist that is highly selective for the ETA receptor (200:1 over ETB receptor). Endothelin 1 (ET1) is a peptide and potent vasoconstrictor. It circulates as an inactive peptide, pro-ET1. Endothelin converting enzymes 1 and 2 (ECE1, ECE2) are expressed by endothelial cells and vascular smooth muscle cells and in neurons in the CNS. They convert the inactive pro-ET1 to the active form, ET1. ET1 can bind to ETA receptor leading to vasocontriction. Ambrisentan can block this interaction. Although there is no evidence that ambrisentan can reduce the risk of Alzheimer's disease or vascular dementia, cerebral hypoperfusion is an early step in dementia and may be exacerbated by activation of the ETA receptor.

Neuroprotective Benefit: No evidence suggests that ambrisentan is beneficial in Alzheimer's disease; however, evidence suggests that ET1 is increased in Alzheimer's or before disease onset suggesting a hypothetical benefit.

Types of evidence:

- 3 observational studies for serum levels of ET1 and risk of dementia
- 1 genetic study connecting ET1 with dementia
- 5 biomarkers studies of ET1 expression in Alzheimer's patients
- 3 animal studies of other ET receptor blockers

Reduced cerebral blood flow is an early event in Alzheimer's disease. Initially, reduced cerebral blood flow was thought to be a consequence of neurodegeneration and structural damage in the brain of Alzheimer's patients, i.e. fewer functioning neurons require less blood flow. However, recent evidence shows increased cerebral oxygen extraction from the blood in early Alzheimer's disease even with concomitant decreased cerebral blood flow. This might suggest that the tissue still needs blood flow, and cerebral hypoperfusion might come before neurodegeneration and actually increase later damage (Love and Miners, 2016).

In addition to cleaving pro-ET1, ECE1 and ECE2 also degrade beta-amyloid. Since beta-amyloid accumulates years before the onset of dementia and cerebral hypoperfusion mirrors the accumulation of beta-amyloid, it is hypothesized that ECE1 and ECE2 may be upregulated in response to increases in beta-amyloid. This may increase the cleavage of pro-ET1 to ET1 which may bind to ETA receptors and cause vasocontriction and reduce blood flow. This may start a feedback loop where cerebral hypoperfusion increases brain damage leading to additional cerebral hypoperfusion (Palmer and Love, 2011).

ETA receptors expressed on vascular smooth muscle cells (VSMCs) mediate vasocontriction and cell proliferation, whereas ETB receptors on endothelial cells mediate the opposite effects, namely vasodilation and clearance of ET1. Theoretically, an ETA receptor-specific antagonist would be most beneficial in Alzheimer's disease. However, in some diseases such as atherosclerosis and essential hypertension, ETB receptors on VSMCs can mediate vasoconstriction (Ohkita et al, 2012). Both ETA receptor-specific and dual ETA/ETB receptor antagonists are marketed for pulmonary hypertension.

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

In a prospective observational study of 5,347 non-demented individuals analyzed for serum cardiovascular risk factors and future vascular dementia risk, those in the two highest quartiles for levels of the inactive pro-ET1 (68-432pmol/L) were at a greater risk for developing vascular dementia (HR 1.94; 95% CI 1.12-3.36) over 4.6 years (Holm et al, 2017). However, in another prospective observational study of 1,046 non-demented individuals over 7 years, serum ET1 levels were not associated with a decline in MMSE scores (Sharma et al, 2016), though another observational study from the same group in the same patient population found that increased serum ET1 levels were associated with a decline in specific cognitive domains (psychomotor speed and language) (Chi et al, 2017).

ET1 is also genetically associated with dementia. Ma et al (2016) identified a SNP (rs12976445) in miR-125a that increases ET1 expression in human endothelial cells and is associated with an increased risk of dementia after stroke (OR 1.32; 95%CI 1.01-1.74 with CT/TT alleles increasing risk and CC allele protective).

Human research to suggest benefits to patients with dementia:
Palmer et al (2012) reported that ET1 levels are elevated throughout the temporal cortex in Alzheimer's post-mortem brain tissue and in the walls of cerebral blood vessels. In addition, in isolated leptomeningeal blood vessels in Alzheimer's tissue, ET1 levels are elevated, ECE1 levels decreased, but ECE1 activity is increased (Palmer et al, 2013). ET1 is also increased in isolated microvessels from postmortem Alzheimer's brain tissue (Luo and Grammas, 2010).

The myelin associated glycoprotein to proteolipid protein 1 (MAG:PLP1 – proteins associated with myelin) ratio declines in chronically hypoperfused brain tissue. Thomas et al (2015) reported that the

MAG:PLP1 ratio is decreased in the post-mortem cortical tissue of Alzheimer's patients and this is inversely correlated with ET1 levels. In vascular dementia white matter tissue, however, the MAG:PLP1 ratio decreases, but ET1 levels increase (Barker et al, 2014).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

No studies have looked at the effect of ambrisentan in Alzheimer's animal models. Elesber et al (2006) reported that bosentan, an ETA and ETB receptor antagonist, improved endothelium-dependent vasorelaxation in Alzheimer's transgenic mice. Similarly, Khalil et al (2002) reported that BQ-123, an ETA receptor antagonist, reversed impaired vasodilation in an Alzheimer's mouse model. Papadopoulous et al (2010) reported that in mice that overexpress TGF-B1 (a mouse model with vascular pathology similar to Alzheimer's disease), ABT-627, an ETA antagonist, had no effect, but it abolished ET1 induced contraction in aged WT littermates. An ETA antagonist, BQ-123, also reduced lesion size in a mouse model of ischemic stroke and systemic inflammation (Murray et al, 2014).

APOE4 interactions: Unknown.

Aging and related health concerns: In general, it is unclear whether ambrisentan will be beneficial in most age-related disease. However, it might be beneficial in certain age-related conditions where levels of serum pro-ET1 or ET1 levels are increased.

Types of Evidence:

- 1 review on efficacy in pulmonary arterial hypertension
- 3 observational studies on increased risk from serum ET1 levels
- 4 pilot studies on effects of ETA or ETA/ETB receptor antagonists on endothelial function
- 4 preclinical studies on ETA or ETA/ETB receptor antagonists on cardiovascular disease (CVD)

Ambrisentan (5-10mg/day) is approved to treat pulmonary arterial hypertension (PAH). In two phase 3 clinical trials, ambrisentan improved performance on the 6-minute walk test (the distance an individual can walk for 6 minutes) at 12 and 24 weeks, performance that was sustained 1-3 years later. It also improved shortness of breath (Peacock et al, 2015). In combination with the PDE5 inhibitor tadalafil, it further reduced clinical failure (defined as time to first occurrence of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response) by 50% compared to monotherapy (Peacock et al, 2015).

Observational studies in aging and cardiovascular disease

ET1 expression in isolated brachial vascular endothelial cells was greater in healthy older men (55-78 years) than in healthy younger men (18-30 years), while endothelium-dependent dilation was lower in older men than then younger men (Donato et al, 2009).

In a prospective observational study with a 20-year follow up, 82 individuals were divided into high or low plasma values of ET1 (with high value defined as >= 2.7pg/ml). Major cardiac and cerebral events (all-cause death, myocardial infarction, revascularization procedures, and fatal or non-fatal stroke) were much more common in the high group than the low group (95% vs. 5% of individuals, respectively). However, ET1 levels may also be indicative of underlying cardiovascular/vascular dysfunction rather than just a causative effect, as among all evaluated baseline clinical and laboratory variables, hypertension (OR 20.4; 95%CI 3.3-127), high ET1 (OR 1.4; 95%CI 1.0-1.8), and the presence of intima-media thickness or asymptomatic carotid plaque (OR 3.7; 95%CI 1.14-12.1) were independent predictors of future events (Novo et al, 2014).

In patients with stable coronary artery disease, increased levels of C-terminal pro-endothelin 1 were at an increased risk of cardiovascular death or heart failure (HR 1.47; 95%CI 1.15-1.88 per standard deviation increase) (Sabatine et al, 2012). Levels in the 25th-75th percentile were 39.04-57.02 pmol/L. ET1 itself may not be as stable as plasma biomarker as the C-terminal pro-ET1 which also indirectly measures activation of the endothelin system (Wang et al, 2017).

Clinical studies in vascular disease with other ET1 receptor antagonists

Ambrisentan has not been studied in diseases other than PAH.

In diabetic patients with coronary artery disease (CAD), both an ETA receptor antagonist (BQ123) and a dual ETA/ETB receptor antagonist improved endothelium-dependent and endothelium-independent vasodilation (Rafnsson et al, 2014). Similarly, an ETA receptor antagonist (BQ123) with an ETB receptor antagonist (BQ788) improved endothelium-dependent vasodilation in patients with atherosclerosis (Bohm et al, 2005) and in insulin-resistant, but not insulin-sensitive subjects (Shemyakin et al, 2006). ETA receptor blockade alone had no effect in insulin-resistant subjects.

In 9 healthy men, infusion with ET1 – to levels that may be present in end-stage renal disease – increased pulse wave velocity and decreased cardiac output by 18%; co-infusion with an ETA receptor antagonist, clazosentan, prevented these effects (Vuurmans et al, 2003).

Preclinical studies with other ET1 receptor antagonists
In a rabbit model of atherosclerosis, darusentan, an ET1A receptor antagonist, given in a preventative manner (before the onset of a high fat diet), reduced the aortic lesion size by 12%. It also reduced total triglycerides by 30%, reduced LDL cholesterol by 80%, reduced HDL cholesterol by 30%, and reduced serum inflammatory biomarkers (ICAM-1, hs-CRP, MCP-1) (Sun et al, 2013). Darusentan also normalized intima-media thickness and reduced plaque size by 31% in APOE-deficient mice fed a high fat diet and improved endothelium-dependent and –independent relaxation (Barton et al, 1998; Uscio et al, 2002).

In a mouse model of heart failure with preserved ejection fraction (HFpEF), treatment with a dual ET1A/ETB receptor antagonist, macitentan, reduced heart wall thickness after 2 weeks (Valero-Munoz et al, 2016).

Safety: Peripheral edema is a common side effect with ambrisentan. Other potential side effects include nasal congestion and anemia.

Types of evidence:
- Two phase 3 clinical trials

Details:
Ambrisentan increases the risk of peripheral edema (HR 2.02; 95%CI 1.4-2.91) (Wei et al, 2016). This is due to an on-target effect from all ETA receptor antagonists. ETA receptors in the kidneys pull sodium from the blood into the urine which is accompanied by an osmotic loss of water in the blood. However, blocking ETA receptors increases blood volume, which, along with dilation of peripheral blood vessels, may cause peripheral edema. However, it is usually mild to moderate in severity (Kohan and Barton, 2014).

In animal studies ambrisentan was reported as a possible teratogen, so it is not to be used in pregnant women. Also, in patients with idiopathic pulmonary fibrosis, it may increase the risk of disease progression.

Other endothelin receptor antagonists increase the risk of hepatotoxicity (possibly by interaction with ETB receptor), so it is approved with a black box warning. However, in clinical trials of patients with PAH, ambrisentan has not increased liver enzymes, and it actually slightly improved liver function (Wei et al, 2016; Peacock et al, 2015). This might be due to the fact that other ET receptor antagonists block ETA and ETB receptors. Ambrisentan may also cause nasal congestion (Buckley et al, 2011). Anemia is another potential side effect due to systemic vasodilation and intravascular fluid retention (Peacock et al, 2015).

Drug interactions: Major drug interactions include leflunomide and teriflunomide (an immunosuppressive and MS drug), lomitapide and mipomersen (lipid-lowering agents), and tizanidine (muscle relaxing agents). Other drugs with side effects that include peripheral edema or anemia may also interact. There are also a number of moderate drug interactions (drugs.com).

Availability/Dosing:
Ambrisentan has an elimination half-life of 9-15 hours, so it can be taken once/day. Bioavailability is 80% and not affected by food. Steady state concentration is reached after 4 days (Buckley et al, 2011).

Prescribed for peripheral arterial hypertension (PAH) (no generic available), label indicates take 5mg once daily, with or without tadalafil 20mg once daily (for PAH). At 4-weeks if well-tolerated, consider increasing ambrisentan to 10mg or tadalafil to 40mg.

Ambrisentan at lower doses (e.g. 2.5 mg) may provide some of the benefits with fewer of the side effects. Available as a tablet.

Research underway:
Ambrisentan is in clinical trials for a number of pulmonary hypertension studies (clinicaltrials.gov). Other ETA receptor antagonists are being studied also for kidney disease.

Search terms:
Pubmed:
ambrisentan
endothelin 1 + alzheimer, atherosclerosis, cardiovascular, aging
darusentan + alzheimer, atherosclerosis, cardiovascular

Clinicaltrials.gov:
Ambrisentan, sitaxentan, atrasentan, zibotentan

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